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(54) CRF ANTAGONISTIC QUINO- AND QUINAZOLINES

CHINOLIN- UND CHINAZOLIN-DERIVATE ALS CRF ANTAGONISTEN

QUINO- ET QUINAZOLINES ANTAGONISTES CRF

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Description

Background of the invention

[0001] This invention relates to quino- and quinazolines which possess CRF receptor antagonistic properties, to pharmaceutical compositions containing these compounds as active ingredient, and the use thereof in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.

[0002] The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalmi and identified as a 41-amino acid peptide (Vale et al., *Science* 213:1394-1397, 1981). Subsequently, sequences of human and rat CRF were isolated and determined to be identical, but different from ovine CRF in 7 of the 41 amino acid residues (Rivier et al., *Proc. Natl. Acad. Sci. USA* 80:4851, 1983; Shibahara et al., *EMBO J.* 2:775, 1983). CRF has been found to produce profound alterations in endocrine, nervous and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotrophic hormone ("ACTH"), β -endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., *Science* 213:1394-1397, 1981). Briefly, CRF is believed to initiate its biological effects by binding to a plasma membrane receptor which has been found to be distributed throughout the brain (DeSouza et al., *Science* 221:1449-1451, 1984), pituitary (DeSouza et al., *Methods Enzymol.* 124:560, 1986; Wynn et al., *Biochem. Biophys. Res. Comm.* 110:602-608, 1983), adrenals (Udelsman et al., *Nature* 319:147-150, 1986) and spleen (Webster, E.L., and E.B. DeSouza, *Endocrinology* 122:609-617, 1988). The CRF receptor is coupled to a GTP-binding protein (Perrin et al., *Endocrinology* 118: 1171- 1179, 1986) which mediates CRF-stimulated increase in intracellular production of cAMP (Bilezikjian, L.M., and W.W. Vale, *Endocrinology* 113:657-662, 1983).

[0003] In addition to its role in stimulating the production of ACTH and POMC, CRF is also believed to coordinate many of the endocrine autonomic, and behavioral responses to stress, and may be involved in the pathophysiology of affective disorders. Moreover, CRF is believed to be a key intermediary in communication between the immune, central nervous, endocrine and cardiovascular systems (Crofford et al., *J. Clin. Invest.* 90:2555-2564, 1992; Sapolsky et al., *Science* 238:522-524, 1987; Tilders et al., *Regul. Peptides* 5:77-84, 1982). Overall, CRF appears to be one of the pivotal central nervous system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.

[0004] Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment. For example, intracerebroventricular injection of CRF results in behavioral activation (Sutton et al., *Nature* 297:331, 1982), persistent activation of the electroencephalogram (Ehlers et al., *Brain Res.* 2/8332, 1983), stimulation of the sympathoadrenomedullary pathway (Brown et al., *Endocrinology* 110:928, 1982), an increase of heart rate and blood pressure (Fisher et al., *Endocrinology* 110:2222, 1982), an increase in oxygen consumption (Brown et al., *Life Sciences* 30:207, 1982), alteration of gastrointestinal activity (Williams et al., *Am. J. Physiol.* 253:G582, 1987), suppression of food consumption (Levine et al., *Neuropharmacology* 22:337, 1983), modification of sexual behavior (Sirinathsinghi et al., *Nature* 305:232, 1983), and immune function compromise (Irwin et al., *Am. J. Physiol.* 255:R744, 1988). Furthermore, clinical data suggest that CRF may be hypersecreted in the brain in depression, anxiety-related disorders, and anorexia nervosa. (DeSouza, *Ann. Reports in Med. Chem.* 25:215-223, 1990).

[0005] Accordingly, clinical data suggest that CRF receptor antagonists may represent novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF.

[0006] Due to the physiological significance of CRF, the development of further biologically active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.

[0007] CRF receptor antagonists have been reported in for example, WO-94/13676, WO-94/13677, WO-95/33750 and WO-96/35689 which disclose pyrrolopyrimidines, pyrazolo[3,4-d]pyrimidines and substituted purines as CRF receptor antagonists. Aminoquinoline derivatives are described in Michne W.F. et al. *J. Med. Chem.*, 38:2748-2762, 1995, as intermediates for 4-substituted-1,4-dihydroquinolines. German patent DE-2,909,871 discloses substituted quinolines as useful intermediates in the synthesis of nitriles. Other structurally related quinoline derivatives are described in Schroeder E. et al. *Eur. J. Med. Chem. - Chim. Ther.*, 14:499-506, 1979, as non-steroidal antiinflammatory agents and in Wommack J.B. et al. *J. Med. Chem.*, 14:1218-1220, 1971, as antimalarials. Ollis W.D. et al. *J.C.S. Perkin Trans. 1*, 953-956, 1989, discloses 2,4-dimethyl-8-(2-nitrophenyl)-quinoline as an intermediate in the synthesis of heterocyclic betaines. 2,4-Diaminoquinazolines are known from WO 94/18980 having insecticidal activity.

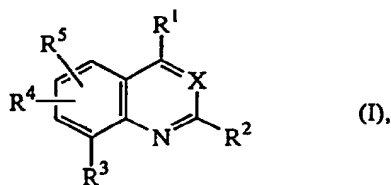
[0008] WO 98/08846 related to certain CRF inhibiting quinoline derivatives is only relevant with respect to novelty under Art. 54(3) EPC.

[0009] The compounds of the present invention differ from the cited art-known compounds structurally, by the nature of the substituents on the quinoline or quinazoline moiety, and pharmacologically by the fact that, unexpectedly, these

compounds have CRF antagonistic properties.

Description of the invention

[0010] This invention concerns CRF antagonistic compounds of formula (I)



including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

X is N or CH;

R¹ is C₁₋₆alkyl, NR⁶R⁷, OR⁷ or SR⁷;

in case X is N then R² is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkylthio;

in case X is CH then R² is C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkylthio;

R³ is Ar¹ or Het¹;

R⁴ and R⁵ are each independently selected from hydrogen, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl, cyano, nitro, amino, and mono- or di(C₁₋₆alkyl)amino;

R⁶ is hydrogen, C₁₋₈alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, C₃₋₆cycloalkyl, C₃₋₆alkenyl, hydroxyC₁₋₆alkyl, C₁₋₆alkylcarbonyloxyC₁₋₆alkyl or C₁₋₆alkoxyC₁₋₆alkyl;

R⁷ is C₁₋₈alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, Ar²CH₂, C₁₋₆alkyloxy-C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₃₋₆alkenyl, thienylmethyl, furanylmethyl, C₁₋₆alkylthioC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylC₁₋₆alkyl;

or R⁶ and R⁷ taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl; and

Ar¹ is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C₁₋₆alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆alkyloxy, benzyloxy, C₁₋₆alkylthio, nitro, amino and mono- or di(C₁₋₆alkyl)amino;

Het¹ is pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, C₁₋₆alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆alkyloxy, benzyloxy, C₁₋₆alkylthio, nitro, amino, and mono- or di(C₁₋₆alkyl)amino; and

Ar² is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, trifluoromethyl;

with the proviso that 2,4-dimethyl-8-(2-nitrophenyl)-quinoline; 4-(1-ethyl-propoxy)-2-methyl-(8-2,4,6-trimethyl-phenyl)-quinoline; (1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethylphenyl)-quinolin-4-yl]-amine; 4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromophenyl)-quinoline; 4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinoline; 4-(1-hydroxymethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-(1-ethylpropylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-diethylamino-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-(ethyl-propyl-amino)-2-methyl-8-(2,4,6-trimethylphenyl)-quinoline; and 4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline are not included.

[0011] This proviso is extended to exclude certain quinoline compounds which have been disclosed by Ollis W.D. et al. in J.C.S. Perkin Trans. I, (5), 953-956 (1989), and in WO 98/08846.

[0012] As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₁₋₆alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof; C₁₋₂alkyl defines straight saturated hydrocarbon radicals having from 1 to 2 carbon atoms such as methyl and ethyl; C₂₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as ethyl, propyl, butyl, 1-methylethyl and the like; C₃₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 3 to 4 carbon atoms such as propyl, butyl, 1-methylethyl and the like; C₁₋₆alkyl includes C₁₋₂alkyl and C₃₋₄alkyl radicals as defined hereinbefore and the higher homologues thereof having from 5 to 6 carbon atoms such as, pentyl, the pentyl isomers, hexyl and the hexyl isomers; C₁₋₈alkyl

includes C₁₋₆alkyl and the higher homologues thereof having from 7 to 8 carbon atoms such as, for example, heptyl, octyl and the like; C₃₋₆alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the like; and where said C₃₋₆alkenyl is linked to a nitrogen or oxygen, the carbon atom making the link preferably is saturated. C₃₋₆cycloalkyl comprises cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. HydroxyC₁₋₆alkyl refers to C₁₋₆alkyl substituted with a hydroxy group.

[0013] The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The compounds of formula (I) which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-amino-salicylic, pantoic and the like acids.

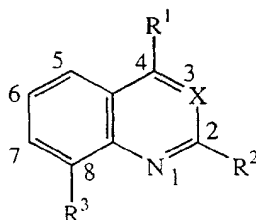
[0014] The term acid addition salts also comprises the hydrates and the solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

[0015] The term stereochemically isomeric forms of compounds of formula (I), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

[0016] Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For instance, compounds of formula (I) wherein Het¹ is pyridinyl substituted with hydroxy, may exist in their corresponding tautomeric form.

[0017] Whenever used hereinafter, the term "compounds of formula (I)" is meant to include also the pharmaceutically acceptable acid addition salts and all stereoisomeric forms.

[0018] The numbering of the bicyclic ring-system present in the compounds of formula (I) is shown below :



[0019] Particular groups of compounds within the invention are those compounds of formula (I) wherein one or more of the radicals have the following meaning :

- a) R¹ is NR⁶R⁷ wherein R⁶ is hydrogen or C₁₋₈alkyl; in particular C₂₋₄alkyl; and R⁷ is C₁₋₈alkyl or C₃₋₆cycloalkylmethyl; in particular C₂₋₄alkyl or cyclopropylmethyl;
- b) R¹ is OR⁷ or SR⁷ wherein R⁷ is C₁₋₆alkyl; in particular C₁₋₄alkyl;
- c) R² is C₁₋₆alkyl; in particular C₁₋₂alkyl;
- d) R³ is a phenyl substituted with 1, 2 or 3 substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkyloxy or halo; wherein the phenyl moiety is preferably substituted in the 3-, 4-, 6-, 2,4- or 2,4,6-positions; or R³ is a pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, amino, nitro, trifluoromethyl, mono- or di(C₁₋₆alkyl)amino, or C₁₋₆alkyl; wherein the pyridinyl moiety preferably is connected via the 2- or 3-position to the remainder of the molecule; and
- e) R⁴ and R⁵ are each independently selected from hydrogen or C₁₋₆alkyl.

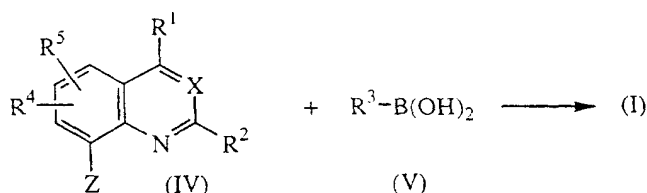
[0020] Preferred compounds are those compounds of formula (I) wherein R¹ is NR⁶R⁷ and R⁶ is C₃₋₄alkyl, preferably propyl; R⁷ is C₃₋₄alkyl or cyclopropylmethyl, preferably propyl; R² is methyl; R³ is a phenyl substituted with 1, 2 or 3

substituents each independently selected from halo, methyl or methoxy; or R^3 is pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, methyl or dimethylamino; and R^4 and R^5 are hydrogen.

[0021] More preferably R^3 is phenyl substituted on the 2- and 4-position with C_{1-2} alkyl or halo; in particular R^3 is 2,4-dichlorophenyl.

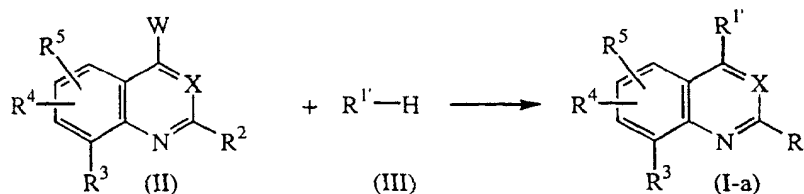
[0022] The most preferred compounds of formula (I) are 2-methyl-4-dipropylamino-8-(2',4'-dichlorophenyl)-quinoline; and 2-methyl-4-(*N*-propyl-*N*-cyclopropanemethyl)amino-8-(2',4'-dichlorophenyl)-quinoline; the stereoisomeric forms and the pharmaceutically acceptable acid addition salts thereof.

[0023] The compounds of the present invention can generally be prepared by reacting an intermediate of formula (IV), wherein Z is bromo or iodo, with an intermediate of formula (V) under Suzuki coupling conditions. Appropriate Suzuki coupling conditions are for example, stirring a solution of an intermediate (IV) and a tetrakis(triphenylphosphine) palladium catalyst in a reaction-inert solvent, e.g. toluene, in the presence of an appropriate base, e.g. sodium carbonate, while adding intermediate (V) dissolved in an alcohol, e.g. ethanol.



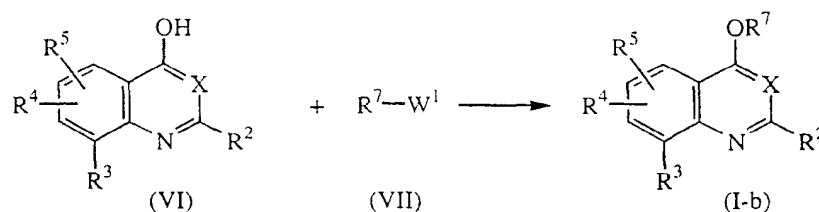
[0024] The above-mentioned Suzuki reaction, i.e. a palladium-catalyzed cross-coupling reaction of a phenylboronic acid derivative with a haloarene in the presence of a base, is extensively described in Suzuki A. et al. *Synthetic Communications*, 11:513-519, 1981 and Suzuki A., *Pure and Applied Chemistry*, 66, 213-222 (1994).

[0025] Compounds of formula (I-a), defined as compounds of formula (I) wherein $R^{1'}$ has the meaning of R^1 other than C_{1-6} alkyl, can be prepared by reacting an intermediate of formula (II) with an intermediate of formula (III). In intermediate (II), W is an appropriate leaving group such as halo, e.g. chloro, bromo, or a sulfonyloxy group, e.g. a mesyloxy or a tosyloxy group.



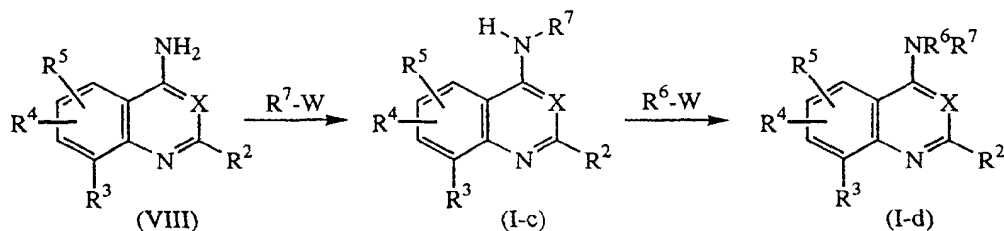
[0026] Said reaction can be performed in a reaction-inert solvent such as, for example, acetonitrile, *N,N*-dimethylformamide, methyl isobutylketone, tetrahydrofuran or dichloromethane; and in the presence of a suitable base such as, for example, sodium carbonate, sodium hydrogen carbonate or triethylamine. When the intermediates of formula (III) are volatile amines, said reaction may also be performed in a sealed reaction vial. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between room temperature and reflux temperature.

[0027] Compounds of formula (I) wherein R^1 is OR^7 , said compounds being represented by formula (I-b), may be prepared by *O*-alkylating an intermediate of formula (VI) with an intermediate of formula (VII), wherein W^1 is an appropriate leaving group such as halo, e.g. chloro, bromo, or a sulfonyloxy group, e.g. a mesyloxy or a tosyloxy group.

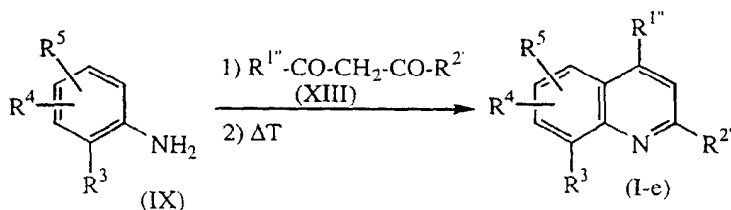


[0028] Said reaction for preparing compounds of formula (I-b) can be performed in a reaction-inert solvent such as, for example, N,N-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, preferably at a temperature ranging between room temperature and reflux temperature.

[0029] The compounds of formula (I) wherein R¹ is -NHR⁷, represented by formula (I-c), can be prepared by N-alkylating an intermediate of formula (VIII) with an intermediate of formula R⁷-W, wherein W is as previously defined. Compounds of formula (I-c) can be further N-alkylated with an intermediate of formula R⁶-W, wherein W is as previously defined, yielding compounds of formula (I-d). These N-alkylations are conducted in a reaction-inert solvent such as, for example, an ether e.g. tetrahydrofuran and preferably in the presence of a strong base, e.g. NaH.



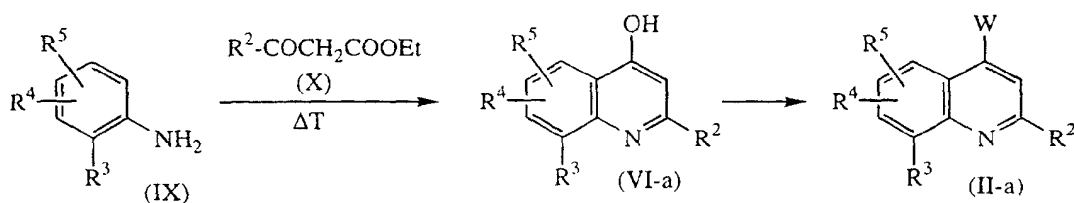
[0030] Compounds of formula (I-e), wherein X is CH and R^{1''} and R^{2'} are C₁₋₆alkyl, can be prepared by reacting an intermediate of formula (IX) with an intermediate of formula (XIII) and subsequent heating in concentrated sulfuric acid.



[0031] Further, compounds of formula (I) may also be converted into each other following art-known functional group transformation procedures.

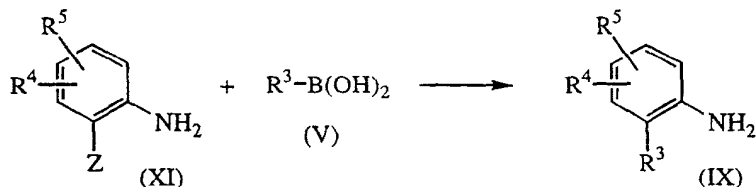
[0032] Intermediates of formula (II) wherein X is CH, said intermediates being represented by formula (II-a), can be prepared as outlined herebelow in scheme I.

Scheme I



[0033] In scheme I, intermediates of formula (IX) are reacted with intermediates of formula (X) and subsequently heated, thereby yielding intermediates of formula (VI-a), in which the hydroxy group is converted into leaving group W, e.g. by treating said intermediates (VI-a) with methanesulfonyloxy chloride or a halogenating reagent such as, e.g. SOCl₂ or POCl₃, thus yielding intermediates of formula (II-a). Said intermediates of formula (VI-a) are intermediates of formula (VI) wherein X is CH.

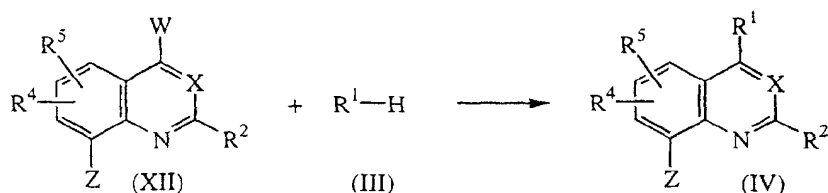
[0034] Intermediates of formula (IX) can be prepared by treating intermediates of formula (XI), wherein Z is as previously described, with an intermediate of formula (V) under Suzuki coupling conditions.



[0035] Intermediates of formula (IX) can also be prepared by reacting an analogue of intermediate (XI) wherein the amino group is replaced by a nitro group, with intermediate (V) under Suzuki coupling conditions, and subsequent conversion of the nitro group to an amino group e.g. by hydrogenation using hydrogen gas and a suitable catalyst such as palladium-on-carbon.

[0036] Also, intermediates of formula (IX) can also be prepared by reacting an analogue of intermediate (XI) wherein the amino group is replaced by a carboxyl group, with intermediate (V) under Suzuki coupling conditions, and subsequent conversion of the carboxyl group to an amino group.

[0037] Intermediates of formula (IV) can generally be prepared by reacting an intermediate of formula (XII), wherein Z is as previously described, with an intermediate of formula (III). Said reaction can be performed as previously described for the synthesis of compounds of formula (I).



[0038] Intermediates of formula (VIII) are prepared by treating intermediates of formula (II) with ammonia.

[0039] Compounds of formula (I) and some of the intermediates may have one or more stereogenic centers in their structure, present in a R or a S configuration.

[0040] The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized as a mixture of stereoisomeric forms, in particular in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

[0041] The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (*J. Neuroscience* 7:88, 1987) and Battaglia et al. (*Synapse* 1:572, 1987). As mentioned above, suitable CRF antagonists include compounds which demonstrate CRF receptor affinity. CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (e.g. [¹²⁵I]tyrosine CFR) to receptor (e.g., receptors prepared from rat cerebral cortex membranes). The radioligand binding assay described by DeSouza et al. (*supra*, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the IC₅₀ as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a "K_i" value calculated by the following equation :

$$K_i = \frac{IC_{50}}{1 + L/K_D}$$

where L = radioligand and K_D = affinity of radioligand for receptor (Cheng and Prusoff, *Biochem. Pharmacol.* 22:3099, 1973).

In addition to inhibiting CRF receptor binding, a compound's CRF receptor antagonist activity may be established by the ability of the compound to antagonize an activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylate cyclase activity. Therefore, compounds may be evaluated as CRF antagonists by their ability to antagonize CRF-stimulated adenylate cyclase activity by, for example, measuring cAMP levels. The CRF-stimulated adenylate cyclase activity assay described by Battaglia et al. (*supra*, 1987) provides an assay for determining a compound's ability to antagonize CRF activity. Accordingly, CRF receptor antagonist activity may be determined by assay techniques which generally include an initial binding assay (such as disclosed by DeSouza (*supra*, 1987)) followed by a cAMP screening protocol (such as disclosed by Battaglia (*supra*, 1987)). With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a K_i of less than 10 μ M. In a preferred embodiment of this invention, a CRF receptor antagonist has a K_i of less than 1 μ M, and more preferably less than 0.25 μ M (*i.e.*, 250 nM).

The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurologic disorders or illnesses. More specifically, the CRF receptor antagonists of the present invention may be useful in treating physiological conditions or disorders arising from the hypersecretion of CRF. Because CRF is believed to be a pivotal neurotransmitter that activates and coordinates the endocrine, behavioral and automatic responses to stress, the CRF receptor antagonists of the present invention can be used to treat neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by the CRF receptor antagonists of this invention include affective disorders such as depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, cardiovascular abnormalities such as unstable angina and reactive hypertension; and feeding disorders such as anorexia nervosa, bulimia, and irritable bowel syndrome. CRF antagonists may also be useful in treating stress-induced immune suppression associated with various diseases states, as well as stroke. Other uses of the CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).

[0042] In another embodiment of the invention, pharmaceutical compositions containing one or more CRF receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a CRF receptor antagonist of the present invention (*i.e.*, a compound of structure (I)) and a pharmaceutically acceptable carrier and/or diluent. The CRF receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder, that is, in an amount sufficient to achieve CRF receptor antagonist activity, and preferably with acceptable toxicity to the patient. Preferably, the pharmaceutical compositions of the present invention may include a CRF receptor antagonist in an amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

[0043] Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a CRF receptor antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the CRF receptor antagonist in an appropriate manner, and in accordance with accepted practices.

[0044] In another embodiment, the present invention provides the use of the compounds as defined in claim 10 for the manufacture of a medicament for treating physiological conditions or disorders arising from the hypersecretion of corticotropin-releasing factor (CRF). Such use includes administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the disorder or illness. The use according to the invention includes systemic administration of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition.

[0045] As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorings, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable ad-

ditives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain, in addition to the CRF receptor antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

[0046] As mentioned above, administration of a compound of the present invention can be used to treat a wide variety of disorders or illnesses. In particular, the compounds of the present invention may be administered to a warm-blooded animal for the treatment of depression, anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, unstable angina, reactive hypertension, anorexia nervosa, bulimia, irritable bowel syndrome, stress-induced immune suppression, stroke, inflammation, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

[0047] The following examples are provided for purposes of illustration, not limitation.

Experimental part

[0048] Hereinafter "THF" means tetrahydrofuran and "DCM" means dichloromethane.

A. Preparation of the intermediates.

Example A.1

[0049]

a) To a stirring solution of 2-bromoaniline (4.0 g) in 120 ml of toluene was added tetrakis(triphenylphosphine) palladium(0) (2.7g, 2.33 mmol, 10% mol) and 2.0M aqueous sodium carbonate solution (35 ml, 70 mmol). In a separate flask, dichlorobenzeneboronic acid (5.0 g) was dissolved in ethyl alcohol (35 ml). To the boronic acid solution was added the 2-bromoaniline mixture. The resulting mixture was heated to reflux overnight. The reaction mixture was cooled, diluted with ethyl acetate and washed with saturated ammonium chloride solution. The organic layer was dried, filtered, concentrated. The residue was purified by flash chromatography on silica gel yielding 2-amino-(2',4'-dichloro)biphenyl (intermediate (7)) (4.8 g). 300 MHz ¹H NMR (CDCl₃): δ 3.54 (br s, 2H), 6.78 (d, 1H), 6.84 (d, 1H), 7.01 (d, 1H), 7.19-7.35 (m, 3H), 7.53 (d, 1H).

b) A solution of intermediate (7) (4.71g), ethyl acetoacetate (2.58 g) and 20 mg of p-toluenesulfonic acid monohydrate in 100 ml of benzene was refluxed 30 minutes. The reaction mixture was cooled, concentrated and purified by flash chromatography on silica gel yielding intermediate (8) (4.5g). 300 MHz ¹H NMR (CDCl₃): δ 1.21 (t, 3H), 1.86 (s, 3H), 4.04 (q, 2H), 4.57 (s, 1H), 7.18 (s, 1H), 7.25-7.43 (m, 5H), 7.47 (d, 1H), 9.89 (s, 1H).

c) A solution of intermediate (8) (2.34g) in 5 ml of diphenylether was added to 10 ml diphenylether at 240°C and the solution was heated to reflux for 5 minutes. The reaction mixture was cooled and the solid was collected by filtration, and rinsed with diethyl ether, yielding 2-methyl-4-hydroxy-8-(2',4'-dichlorophenyl)quinoline (intermediate 9) as a white crystalline solid (1.33g). 300 MHz ¹H NMR (CDCl₃): δ 2.56 (s, 3H), 6.11 (s, 1H), 7.34-7.44 (m, 4H), 7.58 (d, 1H), 8.38 (d, 1H), 8.82 (s, 1H).

d) A mixture of intermediate (9) (1.32g) and phosphorous oxychloride (5 ml) was refluxed for 2 hours, cooled, poured onto ice and neutralized by 1N NaOH. The aqueous layer was extracted by ethyl acetate. The organic layer was washed with brine, dried, concentrated, yielding 2-methyl-4-chloro-8-(2',4'-dichlorophenyl)quinoline (intermediate 1) (1.31mg). 300 MHz ¹H NMR (CDCl₃): δ 2.58 (s, 3H), 7.34 (s, 2H), 7.39 (s, 1H), 7.53 (s, 1H), 7.63-7.65 (m, 2H), 8.26 (dd, 1H).

Example A.2

[0050]

a) A mixture of 2-amino-3-bromo-5 methyl benzoic acid (1 g) and formamide (0.6 ml) was placed in a 1 ml pressure vial and heated to 145°C. After heating for 1 hour, the vial was cooled to room temperature, and 50 ml water was added. The solid white mass was then filtered off and recrystallized from methanol, yielding intermediate (10) (1.01g).

b) A mixture of intermediate (10) (1g) was refluxed in 4 ml POCl₃ for 2 hours. After refluxing, the reaction was cooled and poured onto 50 ml ice. The aqueous solution was made basic with sodium bicarbonate and extracted with ethyl acetate. The organic layers were combined, dried and concentrated, yielding intermediate (11) which was used in the next step without purification.

c) Intermediate (11) was refluxed in the presence of 5 ml dipropyl amine for 1 hour. The reaction was diluted with water and extracted with ethyl acetate. The organic layer was combined, dried and concentrated, yielding a residue

which was dissolved in ethylacetate and run through a plug of silica. Evaporation yielded intermediate (6) (0.4 g).

Example A.3

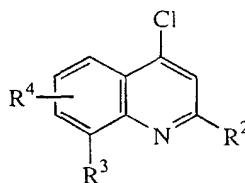
[0051]

a) A mixture of 4'-chloro-6-methoxy-2-biphenylcarboxylic acid (1.2 g), prepared according to the procedure of Meyers A.I. et al. in *J. Org. Chem.* 43:1372-1379 (1978), triethylamine (1.1 ml), diphenylphosphoryl azide (1.2 ml) and tert-butyl alcohol (80 ml) was placed in a 250 ml flask under nitrogen atmosphere. The solution was stirred and refluxed for 5 hours. After reflux, the reaction mixture was cooled and concentrated, yielding a residue which was suspended in diethyl ether. A solid by-product was filtered off and the mother liquid was concentrated, yielding 1.4 g of intermediate (12).

b) Intermediate (12) was dissolved in THF (60 ml), water (12 ml) and concentrated HCl (12 ml) and refluxed for 2 hours. The solution was concentrated and the residue was partitioned between ethyl acetate and water. The organic layer was separated, dried and concentrated, yielding intermediate (13).

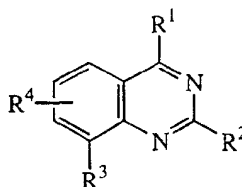
c) Intermediate (13) was suspended in benzene (100 ml) in the presence of ethyl acetoacetate (2 ml) and refluxed using a dean stark trap for 3 hours. The reaction mixture was concentrated and the residue was added to an already hot solution (200°C) of diphenyl ether (20 ml). This reaction mixture was allowed to stir for 15 minutes, cooled and slowly triturated with diethyl ether (200 ml), yielding intermediate (14). c) Intermediate (14) (400 mg) was suspended in phosphorus oxychloride (2 ml) and heated to reflux for 2 hours. The reaction mixture was cooled and poured onto 100 ml of ice. The mixture was partitioned between ethyl acetate (200 ml) and an aqueous saturated sodium bicarbonate solution. The organic layer was separated, dried, an concentrated, yielding 4-chloro-7-methoxy-2-methyl-8-(4'-chlorophenyl)quinoline intermediate (5).

Table I-1 :



Intm. No.	Ex. No.	R ²	R ⁴	R ³
1	A.1	CH ₃	H	2,4-dichlorophenyl
2	A.1	CH ₃	H	2,4,6-trimethylphenyl
3	A.1	CH ₃	7-CH ₃	2-chlorophenyl
4	A.1	CH ₃	7-CH ₃	2,4-dichlorophenyl
5	A.3	CH ₃	7-CH ₃ O	4-chlorophenyl

Table I-2 :



Intm. No.	Ex. No.	R ¹	R ²	R ⁴	R ³
6	A.2	-N(CH ₂ CH ₂ CH ₃) ₂	H	7-CH ₃	Br

B. Preparation of the final compounds.

Example B.1

[0052] A mixture of intermediate (1) (0.1g) and p-toluenesulfonic acid monohydrate (160 mg) in 0.4 ml of dipropylamine in a 3 ml reacti-vials was refluxed at 180°C for 48 hours. The reaction mixture was cooled, partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, concentrated, purified on a preparative TLC plate (hexane/EtOAc, 10:1). Compound (1) was isolated as a pale yellow oil (80 mg).

Example B.2

[0053] A solution of intermediate (1) (20 mg) in 0.5 ml of dimethylsulfoxide in a 1 ml reacti-vials was refluxed at 180°C for 12 hours. The reaction mixture was cooled, partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, concentrated, purified on a preparative TLC plate (hexane/EtOAc, 10:1). Compound (20) was isolated as a colorless oil.

Example B.3

[0054] Intermediate (5) (0.4 g) and palladium tetraphenylphosphine (40 mg) were dissolved in 10 ml toluene and added to a solution of 2,4-dichlorophenyl boronic acid (490 mg) in ethanol (3 ml). To this was added a 2M solution of sodium carbonate (3 ml) and the resulting mixture was refluxed under nitrogen for 15 hours. After refluxing, the solution was cooled and extracted with diethyl ether (100 ml). The ether layer was dried, concentrated and purified on silica (1: 9 ether:hexanes) yielding compound (19).

Example B.4

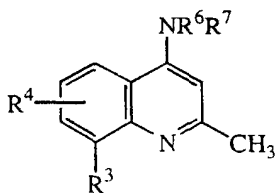
[0055]

a) A mixture of intermediate (7) (1.08 g), 2,4-pentanedione (908 mg) and calcium sulfate (2 g) was heated at 100°C overnight. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, filtered and concentrated. The crude product was purified by flash chromatography on silica gel to provide 1.2 g (83%) of intermediate (15).

b) A solution of intermediate (15) (0.5 g) in concentrated sulphuric acid (5 ml) was heated overnight at 100°C. The reaction mixture was cooled and basified by adding 6N NaOH and extracted with ethyl acetate. The organic layer was washed with an aqueous saturated sodium bicarbonate solution, washed with brine, dried, filtered and evaporated. The residue was purified by flash chromatography on silica gel, yielding 0.4 g (85%) of 2,4-dimethyl-8-(2', 4'-dichlorophenyl)quinoline (compound 22).

[0056] Table F-1 to F-2 list the intermediates that were prepared according to one of the above Examples and table F-3 lists the analytical data for these compounds.

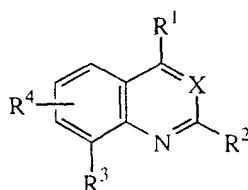
Table F-1 :



Co. No.	Ex. No.	R ⁴	R ⁶	R ⁷	R ³
1	B.1	H	n-propyl	n-propyl	2,4-dichlorophenyl
2	B.1	H	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
3	B.1	H	n-propyl	n-propyl	phenyl
4	B.1	H	n-propyl	cyclopropylmethyl	phenyl
5	B.1	H	hydrogen	3-heptyl	phenyl
6	B.1	H	2-methoxyethyl	2-methoxyethyl	2,4-dichlorophenyl
7	B.1	H	ethyl	n-butyl	2,4-dichlorophenyl
8	B.1	H	n-propyl	phenylmethyl	2,4-dichlorophenyl
9	B.1	H	n-propyl	n-propyl	4-methoxyphenyl
10	B.1	7-CH ₃ O	n-propyl	n-propyl	4-chlorophenyl
11	B.1	7-CH ₃	n-propyl	n-propyl	2-chlorophenyl
12	B.1	H	n-propyl	n-propyl	4-methylphenyl
13	B.1	7-CH ₃	2-methoxyethyl	2-methoxyethyl	2,4-dichlorophenyl
14	B.1	7-CH ₃	n-propyl	cyclopropylmethyl	2,4-dichlorophenyl
15	B.1	7-CH ₃	n-propyl	n-propyl	2,4-dichlorophenyl
16	B.1	H	n-propyl	cyclopropylmethyl	2,4,6-trimethylphenyl
17	B.1	H	n-propyl	n-propyl	2,4,6-trimethylphenyl
18	B.1	H	2-methoxyethyl	2-methoxyethyl	2,4,6-trimethylphenyl
23	B.1	H	ethyl	n-butyl	2,4,6-trimethylphenyl
24	B.1	H	n-propyl	phenylmethyl	2,4,6-trimethylphenyl
25	B.1	H	n-propyl	n-butyl	2,4,6-trimethylphenyl
26	B.1	H	n-propyl	n-propyl	4-trifluoromethylphenyl
27	B.1	H	n-propyl	n-propyl	4-chlorophenyl
28	B.1	H	n-propyl	n-propyl	2,6-dichloro-3-pyridinyl

Co. No.	Ex. No.	R ⁴	R ⁶	R ⁷	R ³
29	B.1	H	n-propyl	n-propyl	6-dimethylamino-2-chloro-3-pyridinyl
30	B.1	H	n-propyl	n-propyl	4,6-dimethoxyphenyl
31	B.1	H	n-propyl	n-propyl	2-dimethylamino-4-methyl-5-pyridinyl
32	B.1	H	n-propyl	n-propyl	2-dimethylamino-4,6-dimethyl-5-pyridinyl

Table F-2 :



Co. No.	Ex. No.	X	R ¹	R ²	R ⁴	R ³
19	B.3	N	-N(CH ₂ CH ₂ CH ₃) ₂	H	7-CH ₃	2,4-dichlorophenyl
20	B.2	CH	-S-CH ₃	CH ₃	H	2,4-dichloromethyl
21	B.2	CH	-OCH ₃	CH ₃	H	2,4-dichlorophenyl
22	B.4	CH	-CH ₃	CH ₃	H	2,4-dichlorophenyl

Table F-3 :

Analytical data		
Co. No.	¹ H NMR data (CDCl ₃)	MS M ⁺
1	δ 0.89 (t, 6H), 1.56-1.66 (m, 4H), 2.52 (s, 3H), 3.25 (t, 4H), 6.73 (s, 1H), 7.33 (d, 1H), 7.36 (d, 1H), 7.43 (d, 1H), 7.49 (d, 1H), 7.52 (s, 1H), 8.11 (d, 1H)	-
2	δ 0.07-0.08 (m, 2H), 0.47-0.50 (m, 2H), 0.92 (t, 3H), 0.95-1.05 (m, 1H), 1.58-1.66 (m, 2H), 2.53 (s, 3H), 3.20 (d, 2H), 3.40 (t, 2H), 6.80 (s, 1H), 7.33 (d, 1H), 7.36 (d, 1H), 7.40 (d, 1H), 7.49 (d, 1H), 7.52 (s, 1H), 8.14 (d, 1H)	-
3	δ 0.89 (t, 6H), 1.58-1.66 (m, 4H), 2.60 (s, 3H), 3.25 (t, 4H), 6.77 (s, 1H), 7.37-7.46 (m, 4H), 7.62 (d, 1H), 7.76 (d, 2H), 8.06 (d, 1H)	-
4	δ 0.07-0.09 (m, 2H), 0.47-0.50 (m, 2H), 0.92 (t, 3H), 0.95-1.05 (m, 1H), 1.58-1.66 (m, 2H), 2.61 (s, 3H), 3.20 (d, 2H), 3.39 (t, 2H), 6.84 (s, 1H), 7.37-7.49 (m, 4H), 7.64 (d, 1H), 7.77 (d, 2H), 8.09 (d, 1H)	-
6	δ 3.32 (s, 6H), 3.55 (t, 4H), 3.59 (t, 3H), 0.92 (t, 3H), 6.88 (s, 1H), 7.30 (d, 1H), 7.32 (d, 1H), 7.44 (t, 1H), 7.51 (s, 1H), 7.52 (d, 1H), 8.18 (d, 1H)	-
7	δ 0.87-0.92 (m, 6H), 1.15 (m., 2H), 1.28-1.35 (m, 2H), 2.53 (s, 3H), 3.25 (t, 2H), 3.36 (q, 3H), 6.73 (s, 1H), 7.31 (d, 1H), 7.37 (d, 1H), 7.43 (t, 1H), 7.50 (d, 1H), 7.51 (s, 1H), 8.07 (d, 1H)	-

Table F-3 : (continued)

Analytical data		
Co. No.	¹ H NMR data (CDCl ₃)	MS M ⁺
9	δ 0.88 (t, 6H), 1.57-1.62 (m, 4H), 2.60 (s, 3H), 3.23 (t, 4H), 3.88 (t, 3H), 6.76 (s, 1H), 7.01 (d, 2H), 7.42 (t, 1H), 7.61 (d, 1H), 7.72 (d, 2H), 8.02 (d, 1H)	-
10	δ 0.87 (t, 3H), 1.59-1.65 (m, 2H), 3.17 (t, 2H), 4.49 (s, 2H), 6.73 (s, 1H), 7.28-7.34 (m, 6H), 7.35 (d, 1H), 7.42 (t, 1H), 7.52 (s, 1H), 7.53 (d, 1H), 8.20 (d, 1H)	-
10	δ 0.89 (m, 6H), 1.59-1.62 (m, 4H), 2.5 (s, 3H), 3.2 (m, 4H), 3.86 (t, 3H), 6.64 (s, 1H), 7.26 (d, 1H), 7.44 (m, 4H), 8.05 (d, 1H)	-
11	δ 2.2 (s, 3H), 2.44 (s, 3H), 6.66 (s, 1H), 7.26 (m, 1H), 7.33 (m, 3H), 7.5 (m, 1H), 7.98 (d, 1H)	366
14	δ 2.20 (s, 3H), 2.44 (s, 3H), 6.66 (s, 1H), 7.26 (m, 1H), 7.33 (m, 3H), 7.5 (m, 1H), 7.98 (d, 1H)	-
19	-	389
20	δ 2.57 (s, 3H), 2.61 (s, 3H), 6.99 (s, 1H), 7.32-7.35 (m, 2H), 7.49-7.60 (m, 3H), 8.13 (d, 1H)	-
22	δ 2.55 (s, 3H), 2.61 (s, 3H), 7.12 (s, 1H), 7.31 (d, 1H), 7.36 (d, 1H), 7.51 (s, 1H), 7.54 (t, 1H), 7.58 (d, 1H), 8.02 (d, 1H)	301
23	δ 0.92 (t, 3H), 1.18 (t, 3H), 1.33-1.38 (m, 2H), 1.58-1.64 (m, 2H), 1.91 (s, 3H), 2.38 (s, 3H), 2.52 (s, 3H), 3.29 (t, 2H), 3.38 (q, 2H), 6.71 (s, 1H), 6.99 (s, 2H), 7.26 (s, 1H), 7.34 (d, 1H), 7.42 (t, 1H), 8.01 (d, 1H)	360
24	δ 0.88 (t, 3H), 1.63-1.68 (m, 2H), 1.92 (s, 6H), 2.38 (s, 3H), 2.49 (s, 3H), 3.19 (t, 2H), 4.51 (s, 2H), 6.71 (s, 1H), 6.99 (s, 2H), 7.28 - 7.31 (m, 1H), 7.33 - 7.37 (m, 5H), 7.42 (dd, 1H), 8.13 (d, 1H)	408
25	δ 0.91 (t, 6H), 1.31 - 1.35 (m, 4H), 1.57 - 1.62 (m, 4H), 1.91 (s, 6H), 2.38 (s, 3H), 2.51 (s, 3H), 3.30 (t, 2H), 6.70 (s, 1H), 6.99 (s, 2H), 7.34 (d, 1H), 7.40 (dd, 1H), 8.01 (dd, 1H)	388
26	-	386
27	-	352
28	δ 0.89 (t, 6H), 1.56 - 1.66 (m, 4H), 2.61 (s, 3H), 3.26 (t, 4H), 6.80 (s, 1H), 7.45 (dd, 1H), 7.62 (dd, 1H), 7.69 (s, 2H), 8.14 (dd, 1H)	388
29	δ 0.88 (t, 6H), 1.56 - 1.64 (m, 4H), 2.62 (s, 3H), 3.13 (s, 6H), 3.26 (t, 4H), 6.77 (s, 1H), 6.84 (s, 1H), 6.90 (s, 1H), 7.43 (dd, 1H), 7.63 (d, 1H), 8.08 (d, 1H)	396
30	δ 1.61 (m, 4H), 2.53 (s, 3H), 3.22 (t, 4H), 3.73 (s, 3H), 3.88 (s, 3H), 6.62 (s, 1H), 6.71 (s, 1H), 7.38 (m, 4H), 7.58 (dd, 1H), 8.04 (dd, 1H)	-
31	δ 0.88 (t, 6H), 1.61 (m, 4H), 2.06 (s, 3H), 2.53 (s, 3H), 3.13 (s, 6H), 3.22 (t, 4H), 6.47 (s, 1H), 6.72 (s, 1H), 7.42 (m, 2H), 8.04 (dd, 1H), 8.09 (dd, 1H)	
32	δ 1.63 (m, 4H), 1.89 (s, 3H), 2.07 (s, 3H), 2.50 (s, 3H), 3.13 (s, 6H), 3.22 (t, 4H), 6.39 (s, 1H), 6.72 (s, 1H), 7.40 (m, 2H), 8.04 (d, 1H)	-

C. Pharmacological examples

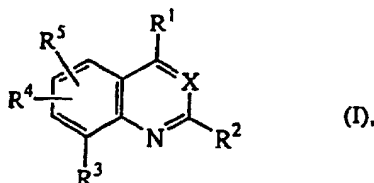
Example C.1 : CRF receptor binding activity

[0057] Compounds were evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by DeSouza et al. (*J. Neurosci.* 7:88-100, 1987). By utilizing various radiolabeled CRF ligands, the assay may be used to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype. Briefly, the binding assay involves the displacement of a radiolabeled CRF ligand from the CRF receptor. More specifically, the binding assay was performed in 1.5 ml Eppendorf tubes using approximately 1×10^6 cells per tube stably transfected with human CRF receptors. Each tube received about 0.1 ml of assay buffer (*e.g.*, Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 20 μ M bacitracin) with or without unlabeled sauvagine, urotensin I or CRF (final concentration, 1 μ M) to determine nonspecific binding, 0.1 ml of [¹²⁵I] tyrosine - ovine CRF (final

concentration approximately 200 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 ml of a membrane suspension of cells containing the CRF receptor. The mixture was incubated for 2 hours at 22°C followed by the separation of the bound and free radioligand by centrifugation. Following two washes of the pellets, the tubes were cut just above the pellet and monitored in a gamma counter for radioactivity at approximately 80% efficiency. All radioligand binding data was analyzed using a non-linear least-square curve-fitting program. Binding activity corresponds to the concentration (nM) of the compound necessary to displace 50% of the radiolabeled ligand from the receptor. Compounds 1, 2, 4, 6 - 11, 20 and 21 were found to have a $K_i \leq 250$ nM.

Claims

1. A compound of formula



including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

X is N or CH;

R¹ is C₁₋₆alkyl, NR⁶R⁷, OR⁷ or SR⁷;

in case X is N then R² is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkylthio;

in case X is CH then R² is C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkylthio;

R³ is Ar¹ or Het¹;

R⁴ and R⁵ are each independently selected from hydrogen, halo, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl, cyano, nitro, amino, and mono- or di(C₁₋₆alkyl)amino;

R⁶ is hydrogen, C₁₋₈alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, C₃₋₆cycloalkyl, C₃₋₆alkenyl, hydroxyC₁₋₆alkyl, C₁₋₆alkylcarbonyloxyC₁₋₆alkyl or C₁₋₆alkoxyC₁₋₆alkyl;

R⁷ is C₁₋₈alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, Ar²CH₂, C₁₋₆alkyloxy-C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₃₋₆alkenyl, thienylmethyl, furanylmethyl, C₁₋₆alkylthioC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylC₁₋₆alkyl;

or R⁶ and R⁷ taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl; and Ar¹ is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C₁₋₆alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆alkyloxy, benzyloxy, C₁₋₆alkylthio, nitro, amino and mono- or di(C₁₋₆alkyl)amino;

Het¹ is pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents each independently selected from halo, C₁₋₆alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆alkyloxy, benzyloxy, C₁₋₆alkylthio, nitro, amino, and mono- or di(C₁₋₆alkyl)amino; and

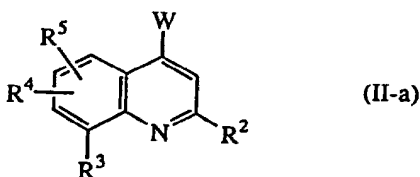
Ar² is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, trifluoromethyl;

with the proviso that 2,4-dimethyl-8-(2-nitrophenyl)-quinoline; 4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; (1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-quinolin-4-yl]-amine; 4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinoline; 4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-chlorophenyl)-quinoline; 4-(1-hydroxymethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-(1-ethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-diethylamino-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-(ethyl-propyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; and 4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline are not included.

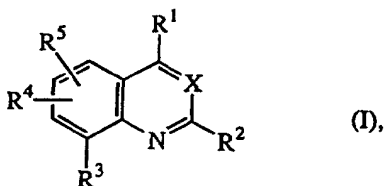
2. A compound according to claim 1 wherein R¹ is OR⁷ or SR⁷ and R⁷ is C₁₋₆alkyl; or R¹ is NR⁶R⁷ and R⁶ is hydrogen or C₁₋₆alkyl, and R⁷ is C₁₋₆alkyl or C₃₋₆cycloalkylmethyl; R² is C₁₋₆alkyl; R³ is a phenyl substituted with 1, 2 or 3 substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkyloxy or halo, or R³ is a pyridinyl substituted with 1, 2 or 3 substituents each independently selected from C₁₋₆alkyl or di(C₁₋₆alkyl)amino; and R⁴ or R⁵ are each

independently selected from hydrogen or C₁₋₆alkyl.

3. A compound according to any of claims 1 to 2 wherein R¹ is NR⁶R⁷ wherein R⁶ is C₂₋₄alkyl and R⁷ is C₂₋₄alkyl or cyclopropylmethyl; R² is C₁₋₂alkyl; R³ is phenyl substituted with 1, 2 or 3 substituents each independently selected from hydrogen, halo or C₁₋₆alkyl.
4. A compound according to any of claims 1 to 2 wherein R¹ is NR⁶R⁷ wherein R⁶ is C₃₋₄alkyl and R⁷ is C₃₋₄alkyl or cyclopropylmethyl; R² is methyl; R³ is 3-pyridinyl substituted on the 4- and/or 6-position with methyl or dimethyl-amino.
5. A compound according to claim 1 wherein the compound is 2-methyl-4-dipropylamino-8-(2',4'-dichlorophenyl)-quinoline; or 2-methyl-4-(N-propyl-N-cyclopropanemethyl)amino-8-(2',4'-dichlorophenyl)-quinoline; a stereoisomeric form or a pharmaceutically acceptable acid addition salt thereof.
6. A composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.
7. A process for preparing a composition as claimed in claim 6 wherein a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5 is intimately mixed with a pharmaceutically acceptable carrier.
8. A compound according to any one of claims 1 to 5 for use as a medicine.
9. A compound of formula (II-a) wherein the radicals X, R², R³, R⁴ and R⁵ are as defined in claim 1 and W is halo, mesyloxy or tosyloxy; a stereoisomeric form or an acid addition salt form thereof



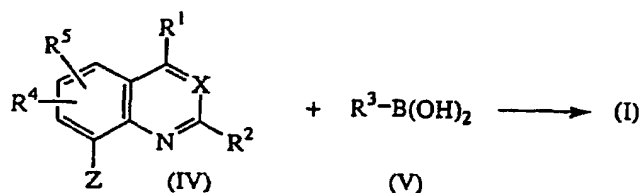
10. The use of compounds of formula



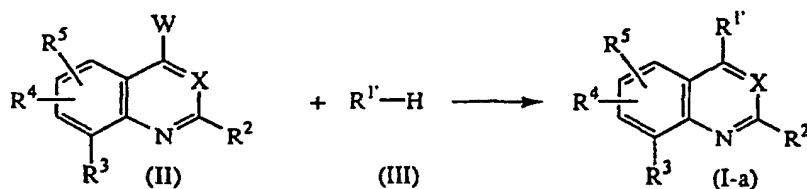
including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein X, R¹, R², R³, R⁴ and R⁵ are as defined in claim 1, including the compound 2,4-dimethyl-8-(2-nitrophenyl)-quinoline, but excluding 4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; (1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-quinolin-4-yl]-amine; 4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinoline; 4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinoline, 4-(1-hydroxymethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-(1-ethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-diethylamino-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; 4-(ethyl-propyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline; and 4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethylphenyl)-quinoline, for the manufacture of a medicament for treating physiological conditions or disorders arising from the hypersecretion of corticotropin-releasing factor (CRF).

11. A process of preparing a compound of formula (I) as claimed in claim I wherein

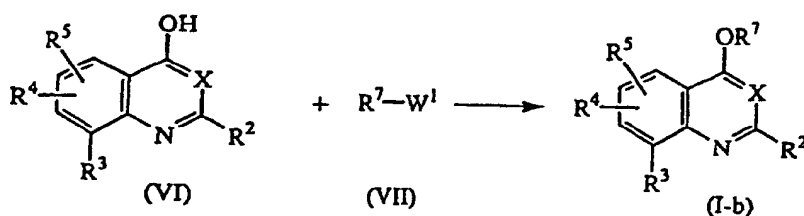
a) intermediates of formula (IV) are reacted with intermediates of formula (V) under Suzuki coupling conditions;



b) an intermediate of formula (II) is reacted with an intermediate of formula (III), wherein R^{1'} has the meaning of R¹ other than C₁₋₆alkyl, thereby yielding compounds of formula (I-a);

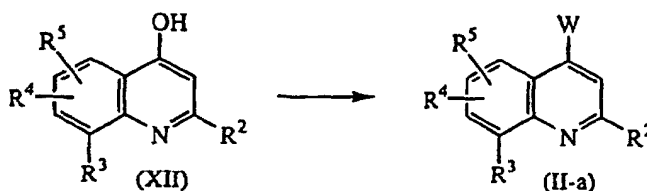


c) an intermediate of formula (VI) is O-alkylated with an intermediate of formula (VII) in a reaction-inert solvent and in the presence of a suitable base, yielding compounds of formula (I-b), defined as compounds of formula (I) wherein R¹ is OR⁷,



wherein in the above reaction schemes the radicals R¹, R², R³, R⁶, R⁷ and X are as defined in claim 1, Z is bromo or iodo and W and W¹ are appropriate leaving groups;
 or, if desired, compounds of formula (I) are converted into each other following art-known transformation reactions;
 and further, if desired, compounds of formula (I) are converted into an acid addition salt by treatment with an acid, or conversely, the acid addition salt forms are converted into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

12. A process of preparing a compound of formula (II-a) as claimed in claim 9 wherein a) an intermediate of formula (IX) is treated with methanesulfonyloxy chloride, benzene-sulfonyloxy chloride or a halogenating reagent such as, e.g. SOCl₂ or POCl₃;



wherein in the above reaction scheme the radicals X, R², R³, R⁴ and R⁵ are as defined in claim 1 and W is halo, mesyloxy or tosyloxy;
 or, if desired, compounds of formula (II-a) are converted into each other following art-known transformation reac-

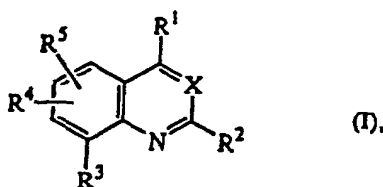
tions; and further, if desired, compounds of formula (II-a) are converted into an acid addition salt by treatment with an acid, or conversely, the acid addition salt forms are converted into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

13. The use according to claim 10 wherein the disorder is selected from depression, an anxiety-related disorder, a feeding disorder, stress-induced immune suppression, stroke, Cushing's disease, infantile spasms, epilepsy, seizure, and inflammatory condition.

14. The use of claim 13 wherein the feeding disorder is anorexia nervosa, bulimia or irritable bowel syndrome.

Patentansprüche

1. Verbindung der Formel



einschließlich der Stereoisomeren und der pharmazeutisch annehmbaren Säureadditionssalzformen derselben, wobei

X N oder CH ist;

R¹ C₁₋₆-Alkyl, NR⁶R⁷, OR⁷ oder SR⁷ ist;

in dem Falle, daß X N ist, R² Wasserstoff, C₁₋₆-Alkyl, C₁₋₆-Alkyloxy oder C₁₋₆-Alkylthio ist;

in dem Falle, daß X CH ist, R² C₁₋₆-Alkyl, C₁₋₆-Alkyloxy oder C₁₋₆-Alkylthio ist;

R³ Ar¹ oder Het¹ ist;

R⁴ und R⁵ unabhängig ausgewählt sind aus Wasserstoff, Halo, C₁₋₆-Alkyl, C₁₋₆-Alkyloxy, Trifluormethyl, Cyano, Nitro, Amino und Mono- oder Di(C₁₋₆-alkyl)amino;

R⁶ Wasserstoff, C₁₋₆-Alkyl, Mono- oder Di(C₃₋₆-cycloalkyl)methyl, C₃₋₆-Cycloalkyl, C₃₋₆-Alkenyl, Hydroxy-C₁₋₆-alkyl, C₁₋₆-Alkylcarbonyloxy-C₁₋₆-alkyl oder C₁₋₆-Alkoxy-C₁₋₆-alkyl ist;

R⁷ C₁₋₈-Alkyl, Mono- oder Di(C₃₋₆-cycloalkyl)methyl, Ar²CH₂, C₁₋₆-Alkyloxy-C₁₋₆-alkyl, Hydroxy-C₁₋₆-alkyl, C₃₋₆-Alkenyl, Thienylmethyl, Furanylmethyl, C₁₋₆-Alkylthio-C₁₋₆-alkyl, Mono- oder Di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl, Di(C₁₋₆-alkyl)amino, C₁₋₆-Alkylcarbonyl-C₁₋₆-alkyl ist;

oder R⁶ und R⁷ zusammengekommen mit dem Stickstoffatom, an das sie gebunden sind, eine Pyrrolidinyl-, Piperidinyl-, Homopiperidinyl- oder Morpholinyl-Gruppe bilden können, fakultativ substituiert mit C₁₋₆-Alkyl oder C₁₋₆-Alkyloxy-C₁₋₆-alkyl; und

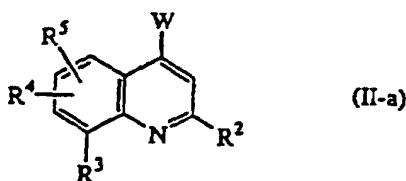
Ar¹ Phenyl ist; Phenyl, substituiert mit 1, 2 oder 3 Substituenten, jeweils unabhängig ausgewählt aus Halo, C₁₋₆-Alkyl, Trifluormethyl, Hydroxy, Cyano, C₁₋₆-Alkyloxy, Benzyloxy, C₁₋₆-Alkylthio, Nitro, Amino und Mono- oder Di(C₁₋₆-alkyl)amino;

Het¹ Pyridinyl ist; Pyridinyl, substituiert mit 1, 2 oder 3 Substituenten, jeweils unabhängig ausgewählt aus Halo, C₁₋₆-Alkyl, Trifluormethyl, Hydroxy, Cyano, C₁₋₆-Alkyloxy, Benzyloxy, C₁₋₆-Alkylthio, Nitro, Amino und Mono- oder Di(C₁₋₆-alkyl)amino; und

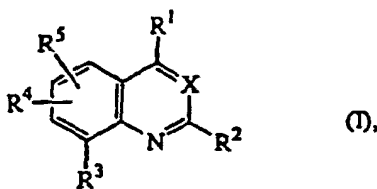
Ar² Phenyl ist; Phenyl, substituiert mit 1, 2 oder 3 Substituenten, jeweils unabhängig ausgewählt aus Halo, C₁₋₆-Alkyl, C₁₋₆-Alkyloxy, Di(C₁₋₆-alkyl)amino-C₁₋₆-alkyl, Trifluormethyl;

mit der Maßgabe, daß 2,4-Dimethyl-8-(2-nitrophenyl)-chinolin; 4-(1-Ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin; (1-Ethyl-propyl)-(2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin-4-yl)-amin; 4-(1-Ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-brom-phenyl)-chinolin; 4-(1-Ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-chlor-phenyl)-chinolin; 4-(1-Hydroxymethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin; 4-(1-Hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin; 4-(1-Ethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin; 4-Diethylamino-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin; 4-(Ethyl-propyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin; und 4-(Butyl-ethylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin nicht eingeschlossen sind.

2. Verbindung nach Anspruch 1, **dadurch gekennzeichnet, daß** R^1 OR^7 oder SR^7 ist und R^7 C_{1-6} -Alkyl ist; oder R^1 NR^6R^7 ist und R^6 Wasserstoff oder C_{1-6} -Alkyl ist, und R^7 C_{1-6} -Alkyl oder C_{3-6} -Cycloalkylmethyl ist; R^2 C_{1-6} -Alkyl ist; R^3 ein Phenyl ist, substituiert mit 1, 2 oder 3 Substituenten, jeweils unabhängig ausgewählt aus C_{1-6} -Alkyl, C_{1-6} -Alkyloxy oder Halo, oder R^3 ein Pyridinyl ist, substituiert mit 1, 2 oder 3 Substituenten, jeweils unabhängig ausgewählt aus C_{1-6} -Alkyl oder $Di(C_{1-6}\text{-alkyl})\text{amino}$; und R^4 oder R^5 jeweils unabhängig ausgewählt sind aus Wasserstoff oder C_{1-6} -Alkyl.
3. Verbindung nach einem der Ansprüche 1 bis 2, **dadurch gekennzeichnet, daß** R^1 NR^6R^7 ist, wobei R^6 C_{2-4} -Alkyl ist und R^7 C_{2-4} -Alkyl oder Cyclopropylmethyl ist; R^2 C_{1-2} -Alkyl ist; R^3 Phenyl ist, substituiert mit 1, 2 oder 3 Substituenten, jeweils unabhängig ausgewählt aus Wasserstoff, Halo oder C_{1-6} -Alkyl.
4. Verbindung nach einem der Ansprüche 1 bis 2, **dadurch gekennzeichnet, daß** R^1 NR^6R^7 ist, wobei R^6 C_{3-4} -Alkyl ist und R^7 C_{3-4} -Alkyl oder Cyclopropylmethyl ist; R^2 Methyl ist; R^3 3-Pyridinyl ist, substituiert an der 4- und/oder 6-Position mit Methyl oder Dimethylamino.
5. Verbindung nach Anspruch 1, **dadurch gekennzeichnet, daß** die Verbindung 2-Methyl-4-dipropylamino-8-(2',4'-dichlorphenyl)-chinolin; oder 2-Methyl-4-(N-propyl-N-cyclopropanmethyl)amino-8-(2',4'-dichlorphenyl)-chinolin; eine stereoisomere Form oder ein pharmazeutisch annehmbares Säureadditionssalz davon ist.
6. Zusammensetzung, die einen pharmazeutisch annehmbaren Trägerstoff und als aktiven Inhaltsstoff eine therapeutisch wirksame Menge einer Verbindung, wie beansprucht in einem der Ansprüche 1 bis 5, umfaßt.
7. Verfahren zur Herstellung einer Zusammensetzung nach Anspruch 6, **dadurch gekennzeichnet, daß** eine therapeutisch wirksame Menge einer Verbindung, wie beansprucht in einem der Ansprüche 1 bis 5, innig mit einem pharmazeutisch annehmbaren Trägerstoff vermischt wird.
8. Verbindung nach einem der Ansprüche 1 bis 5, zur Verwendung als ein Arzneimittel.
9. Verbindung der Formel (II-a), wobei die Reste X , R^2 , R^3 , R^4 und R^5 sind, wie definiert in Anspruch 1, und W Halo, Mesyloxy oder Tosyloxy ist; eine stereoisomere Form oder ein Säureadditionssalz davon



10. Verwendung von Verbindungen der Formel

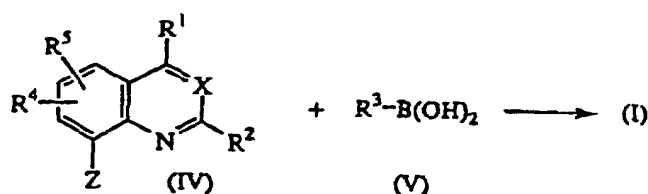


einschließlich der Stereoisomeren und der pharmazeutisch annehmbaren Säureadditionssalzformen derselben, wobei X , R^1 , R^2 , R^3 , R^4 und R^5 sind, wie definiert in Anspruch 1, einschließlich der Verbindung 2,4-Dimethyl-8-(2-nitrophenyl)-chinolin, aber ausschließlich 4-(1-Ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin; (1-Ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin-4-yl]-amin; 4-(1-Ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromphenyl)-chinolin; 4-(1-Ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-chlorphenyl)-chinolin, 4-(1-Hydroxymethyl-propoxy)-2-methyl-8-(2,4,6-trimethylphenyl)-chinolin; 4-(1-Hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethylphenyl)-chinolin; 4-(1-Ethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin; 4-Di-

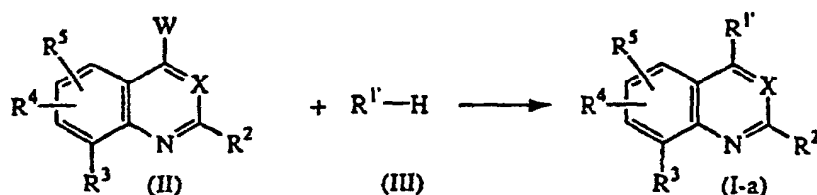
ethylamino-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin; 4-(Ethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin; und 4-(Butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-chinolin, zur Herstellung eines Arzneimittels zur Behandlung physiologischer Zustände oder Störungen, die aus der Hypersekretion von Corticotropin-freisetzendem Faktor (CRF) resultieren.

11. Verfahren zur Herstellung einer Verbindung der Formel (I), wie beansprucht in Anspruch 1, wobei

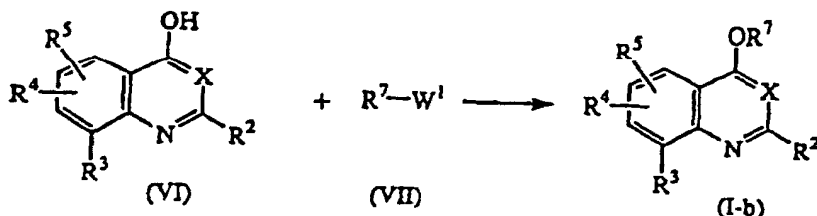
a) Zwischenprodukte der Formel (IV) mit Zwischenprodukten der Formel (V) unter Suzuki-Kopplungsbedingungen umgesetzt werden;



b) ein Zwischenprodukt der Formel (II) mit einem Zwischenprodukt der Formel (III) umgesetzt wird, wobei R^{1'} die Bedeutung von R¹ hat, außer C₁₋₆-Alkyl, wodurch Verbindungen der Formel (I-a) geliefert werden;



c) ein Zwischenprodukt der Formel (VI) O-alkyliert wird mit einem Zwischenprodukt der Formel (VII) in einem reaktionsinerten Lösungsmittel und in Gegenwart einer geeigneten Base, wodurch Verbindungen der Formel (I-b) geliefert werden, definiert als Verbindungen der Formel (I), in denen R¹ OR⁷ ist

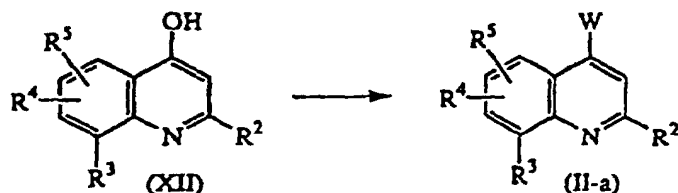


wobei in den obigen Reaktionsschemata die Reste R¹, R², R³, R⁶, R⁷ und X sind, wie definiert in Anspruch 1, Z Brom oder Iod ist und W und W¹ geeignete Abgangsgruppen sind;

oder, falls gewünscht, Verbindungen der Formel (I) ineinander umgewandelt werden unter Befolgung von aus dem Stand der Technik bekannten Umformungsreaktionen; und weiter, falls gewünscht, Verbindungen der Formel (I) in ein Säureadditionssalz umgewandelt werden durch Behandlung mit einer Säure oder umgekehrt die Säureadditionssalzformen umgewandelt werden in die freie Base durch Behandlung mit Alkali; und, falls gewünscht, Herstellen von stereochemisch isomeren Formen derselben.

12. Verfahren zur Herstellung einer Verbindung der Formel (II-a), wie beansprucht in Anspruch 9, wobei

a) ein Zwischenprodukt der Formel (IX) behandelt wird mit Methansulfonyloxychlorid, Benzolsulfonyloxychlorid oder einem Halogenierungsreagens wie etwa z.B. SOCl₂ oder POCl₃;



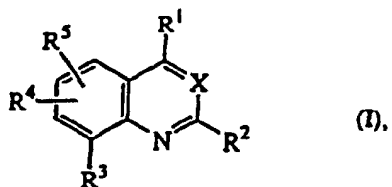
wobei in dem obigen Reaktionsschema die Reste X, R², R³, R⁴ und R⁵ sind, wie definiert in Anspruch 1, und W Halo, Mesyloxy oder Tosyloxy ist;
oder, falls gewünscht, Verbindungen der Formel (II-a) ineinander umgewandelt werden unter Befolgung von aus dem Stand der Technik bekannten Umformungsreaktionen; und weiter, falls gewünscht, Verbindungen der Formel (II-a) in ein Säureadditionssalz umgewandelt werden durch Behandlung mit einer Säure oder umgekehrt die Säureadditionssalzformen umgewandelt werden in die freie Base durch Behandlung mit Alkali; und, falls gewünscht, Herstellen von stereochemisch isomeren Formen derselben.

13. Verwendung nach Anspruch 10, **dadurch gekennzeichnet, daß** die Störung ausgewählt ist aus Depression, einer mit Angstzuständen zusammenhängenden Störung, einer Nahrungsaufnahmestörung, Streß-induzierter Immunsuppression, Schlaganfall, Cushing-Krankheit, infantilen Spasmen, Epilepsie, Krampfanfall und entzündlichem Zustand.

14. Verbindung nach Anspruch 13, **dadurch gekennzeichnet, daß** die Nahrungsaufnahmestörung Anorexia nervosa, Bulimie oder Reizkolon ist.

Revendications

1. Composé de formule



y compris les stéréoisomères et les formes de type sel d'addition d'acide acceptables au plan pharmaceutique de celui-ci, dans laquelle

X est N ou CH ;

R¹ est un groupe alkyle en C₁-C₆, NR⁶R⁷, OR⁷ ou SR⁷ ;

dans le cas où X est N, alors R² est un atome d'hydrogène, un groupe alkyle en C₁-C₆, alkyloxy en C₁-C₆ ou alkylthio en C₁-C₆ ;

dans le cas où X est CH, alors R² est un groupe alkyle en C₁-C₆, alkyloxy en C₁-C₆ ou alkylthio en C₁-C₆ ;

R³ est Ar¹ ou Het¹ ;

R⁴ et R⁵ sont chacun choisis indépendamment parmi un atome d'hydrogène, d'halogène, un groupe alkyle en C₁-C₆, alkyloxy en C₁-C₆, trifluorométhyle, cyano, nitro, amino et mono- ou di(alkyl en C₁-C₆)amino ;

R⁶ est un atome d'hydrogène, un groupe alkyle en C₁-C₈, mono- ou di-(cycloalkyl en C₃-C₆)méthyle, cycloalkyle en C₃-C₆, alcényle en C₃-C₆, hydroxyalkyle en C₁-C₆, (alkyl en C₁-C₆)carbonyloxyalkyle en C₁-C₆ ou (alcoxy en C₁-C₆)alkyle en C₁-C₆ ;

R⁷ est un groupe alkyle en C₁-C₈, mono- ou di-(cycloalkyl en C₃-C₆)méthyle, Ar²CH₂, (alkyloxy en C₁-C₆)alkyle en C₁-C₆, hydroxyalkyle en C₁-C₆, alcényle en C₃-C₆, thiénylméthyle, furanylméthyle, (alkyl en C₁-C₆)thioalkyle en C₁-C₆, mono- ou di-(alkyl en C₁-C₆)aminoalkyle en C₁-C₆, di(alkyl en C₁-C₆)amino, (alkyl en C₁-C₆)carbonylalkyle en C₁-C₆ ;

ou R⁶ et R⁷ pris conjointement à l'atome d'azote sur lequel ils sont fixés peuvent former un groupe pyrrolidinyne,

pipéridinyle, homopipéridinyle ou morpholine, éventuellement substitué par un groupe alkyle en C₁-C₆ ou (alkyloxy en C₁-C₆)alkyle en C₁-C₆ ; et

Ar¹ est un groupe phényle ; phényle substitué par 1, 2 ou 3 substituants chacun choisis indépendamment parmi un atome d'halogène, un groupe alkyle en C₁-C₆, trifluorométhyle, hydroxy, cyano, alkyloxy en C₁-C₆, benzyloxy, alkylthio en C₁-C₆, nitro, amino et mono- ou di-(alkyl en C₁-C₆)amino ;

Het¹ est un groupe pyridinyle ; pyridinyle substitué par 1, 2 ou 3 substituants chacun choisis indépendamment parmi un atome d'halogène, un groupe alkyle en C₁-C₆, trifluorométhyle, hydroxy, cyano, alkyloxy en C₁-C₆, benzyloxy, alkylthio en C₁-C₆, nitro, amino et mono- ou di-(alkyl en C₁-C₆)amino ; et

Ar² est un groupe phényle ; phényle substitué par 1, 2 ou 3 substituants chacun choisis indépendamment parmi un atome d'halogène, un groupe alkyle en C₁-C₆, alkyloxy en C₁-C₆, di(alkyl en C₁-C₆)aminoalkyle en C₁-C₆, trifluorométhyle ; à condition que les composés 2,4-diméthyl-8-(2-nitrophényl)quinoléine ; 4-(1-éthylpropoxy)-2-méthyl-8-(2,4,6-triméthylphényl)quinoléine ; (1-éthylpropyl)-[2-méthyl-8-(2,4,6-triméthylphényl)quinoléin-4-yl]amine ; 4-(1-éthylpropoxy)-2-méthyl-(2,6-diméthyl-4-bromophényl)-quinoléine ; 4-(1-éthylpropoxy)-2-méthyl-(2,6-diméthyl-4-chlorophényl)-quinoléine ; 4-(1-hydroxyméthylpropoxy)-2-méthyl-8-(2,4,6-triméthylphényl)quinoléine ; 4-(1-hydroxyméthylpropylamino)-2-méthyl-8-(2,4,6-triméthylphényl)quinoléine ; 4-(1-éthylpropylamino)-2-méthyl-8-(2,4,6-triméthylphényl)quinoléine ; 4-diéthylamino-2-méthyl-8-(2,4,6-triméthylphényl)quinoléine ; 4-(éthylpropylamino)-2-méthyl-8-(2,4,6-triméthylphényl)-quinoléine ; et 4-(butyléthylamino)-2-méthyl-8-(2,4,6-triméthylphényl)-quinoléine ne soient pas inclus.

2. Composé selon la revendication 1, dans lequel R¹ est OR⁷ ou SR⁷ et R⁷ est un groupe alkyle en C₁-C₆ ; ou R¹ est NR⁶R⁷ et R⁶ est un atome d'hydrogène ou un groupe alkyle en C₁-C₆, et R⁷ est un groupe alkyle en C₁-C₆ ou (cycloalkyl en C₃-C₆)méthyle ; R² est un groupe alkyle en C₁-C₆ ; R³ est un groupe phényle substitué par 1, 2 ou 3 substituants chacun choisis indépendamment parmi un groupe alkyle en C₁-C₆, alkyloxy en C₁-C₆ ou un atome d'halogène, ou R³ est un groupe pyridinyle substitué par 1, 2 ou 3 substituants chacun choisis indépendamment parmi un groupe alkyle en C₁-C₆ ou di(alkyl en C₁-C₆)amino ; et R⁴ ou R⁵ sont choisis chacun indépendamment parmi un atome d'hydrogène ou un groupe alkyle en C₁-C₆.

3. Composé selon l'une quelconque des revendications 1 à 2, dans lequel R¹ est NR⁶R⁷ où R⁶ est un groupe alkyle en C₂-C₄ et R⁷ est un groupe alkyle en C₂-C₄ ou cyclopropylméthyle ; R² est un groupe alkyle en C₁-C₂ ; R³ est un groupe phényle substitué par 1, 2 ou 3 substituants chacun choisis indépendamment parmi un atome d'hydrogène, d'halogène ou un groupe alkyle en C₁-C₆.

4. Composé selon l'une quelconque des revendications 1 à 2, dans lequel R¹ est NR⁶R⁷ où R⁶ est un groupe alkyle en C₃-C₄ et R⁷ est un groupe alkyle en C₃-C₄ ou cyclopropylméthyle ; R² est un groupe méthyle ; R³ est un groupe 3-pyridinyle substitué en position 4 et/ou 6 par un groupe méthyle ou diméthylamino.

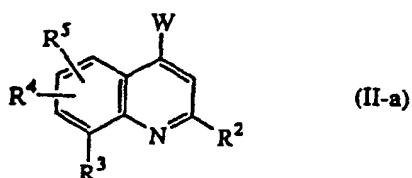
5. Composé selon la revendication 1, dans lequel le composé est la 2-méthyl-4-dipropylamino-8-(2',4'-dichlorophényl)quinoléine ; ou la 2-méthyl-4-(N-propyl-N-cyclopropaneméthyl)amino-8-(2',4'-dichlorophényl)-quinoléine ; ou une forme stéréoisomère ou un sel d'addition d'acide acceptable au plan pharmaceutique de celui-ci.

6. Composition comprenant un véhicule acceptable au plan pharmaceutique et, en tant qu'ingrédient actif, une quantité efficace au plan thérapeutique d'un composé selon l'une quelconque des revendications 1 à 5.

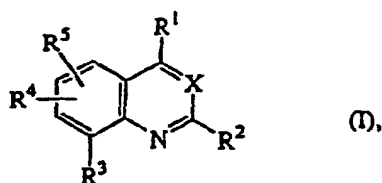
7. Procédé de préparation d'une composition selon la revendication 6, dans lequel une quantité efficace au plan thérapeutique d'un composé selon l'une quelconque des revendications 1 à 5 est intimement mélangée avec un véhicule acceptable au plan pharmaceutique.

8. Composé selon l'une quelconque des revendications 1 à 5 destiné à une utilisation comme médicament.

9. Composé de formule (II-a), dans laquelle les radicaux X, R², R³, R⁴ et R⁵ sont tels que définis dans la revendication 1 et W est un atome d'halogène, un groupe métyloxy ou tosyloxy ; une forme stéréoisomère ou un sel d'addition d'acide de celui-ci



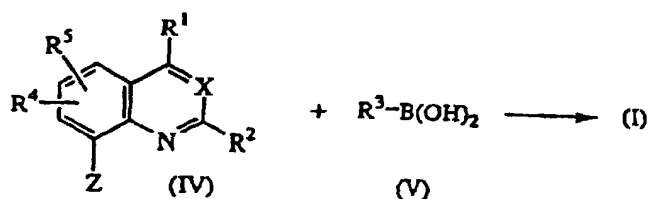
10. Utilisation de composés de formule



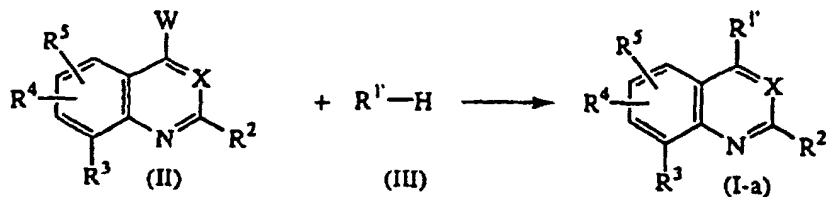
y compris les stéréoisomères et les formes de type sel d'addition d'acide acceptables au plan pharmaceutique de ceux-ci, dans laquelle X, R¹, R², R³, R⁴ et R⁵ sont tels que définis dans la revendication 1, y compris le composé 2,4-diméthyl-8-(2-nitrophényl)quinoléine, mais à l'exclusion de la 4-(1-éthylpropoxy)-2-méthyl-8-(2,4,6-triméthylphényl)-quinoléine ; la (1-éthylpropyl)-[2-méthyl-8-(2,4,6-triméthylphényl)quinoléin-4-yl]aminé ; la 4-(1-éthylpropoxy)-2-méthyl-(2,6-diméthyl-4-bromophényl)-quinoléine ; la 4-(1-éthylpropoxy)-2-méthyl-(2,6-diméthyl-4-chlorophényl)-quinoléine ; la 4-(1-hydroxyméthylpropoxy)-2-méthyl-8-(2,4,6-triméthylphényl)quinoléine ; la 4-(1-hydroxyméthylpropylamino)-2-méthyl-8-(2,4,6-triméthylphényl)quinoléine ; la 4-(1-éthylpropylamino)-2-méthyl-8-(2,4,6-triméthylphényl)quinoléine ; la 4-diéthylamino-2-méthyl-8-(2,4,6-triméthylphényl)quinoléine ; la 4-(éthylpropylamino)-2-méthyl-8-(2,4,6-triméthylphényl)-quinoléine ; et la 4-(butyléthylamino)-2-méthyl-8-(2,4,6-triméthylphényl)-quinoléine, pour la fabrication d'un médicament pour traiter des états ou des troubles physiologiques provenant de l'hypersécrétion du facteur de libération de la corticotropine (CFR).

11. Procédé de préparation d'un composé de formule (I) selon la revendication 1, dans lequel

a) des intermédiaires de formule (IV) sont mis à réagir avec des intermédiaires de formule (V) dans des conditions de couplage de Suzuki ;

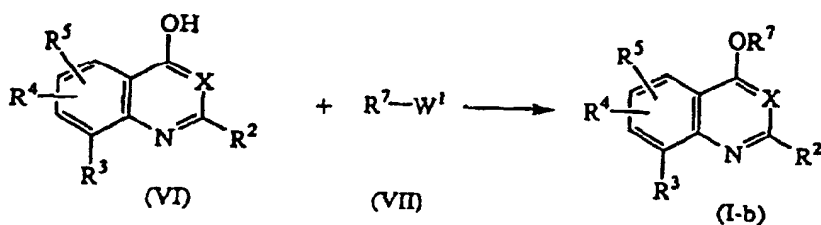


b) un intermédiaire de formule (II) est mis à réagir avec un intermédiaire de formule (III), dans lequel R^{1'} a la signification de R¹ autre qu'un groupe alkyle en C₁-C₆, afin de produire des composés de formule (I-a) ;



c) un intermédiaire de formule (VI) est O-alkylé avec un intermédiaire de formule (VII) dans un solvant inerte vis-à-vis de la réaction et en présence d'une base convenable, pour produire des composés de formule (I-b),

définis comme des composés de formule (I) dans laquelle R^1 est OR^7 ,

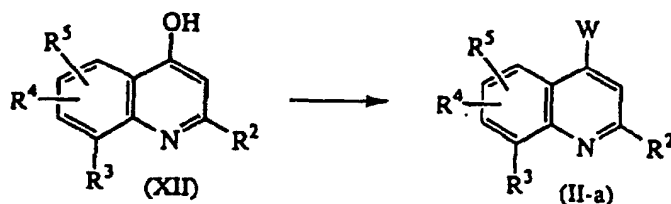


où dans les schémas réactionnels ci-dessus, les radicaux R^1 , R^2 , R^3 , R^6 , R^7 et X sont tels que définis dans la revendication 1, Z est un atome de brome ou d'iode et W et W^1 sont des groupes partants appropriés ;

ou, le cas échéant, les composés de formule (I) sont convertis les uns en les autres par des réactions de transformation connues dans la technique ; et en outre, le cas échéant, les composés de formule (I) sont convertis en un sel d'addition d'acide par un traitement avec un acide ou, en revanche, les formes sel d'addition d'acide sont converties en base libre par un traitement avec une base ; et, le cas échéant, la préparation de formes isomères au plan stoechiométrique de ceux-ci.

12. Procédé de préparation d'un composé de formule (II-a) selon la revendication 9, dans lequel

a) un intermédiaire de formule (IX) est traité avec un chlorure de méthanesulfonyloxy, un chlorure de benzènesulfonyloxy ou un réactif d'halogénéation tel que, par exemple, $SOCl_2$ ou $POCl_3$;



où dans le schéma réactionnel ci-dessus, les radicaux X, R^2 , R^3 , R^4 et R^5 sont tels que définis dans la revendication 1 et W est un atome d'halogène, un groupe mésoxy ou tosyloxy ;

ou, le cas échéant, les composés de formule (II-a) sont convertis les uns en les autres par des réactions de transformation connues dans la technique ; et en outre, le cas échéant, les composés de formule (II-a) sont convertis en un sel d'addition d'acide par un traitement avec un acide ou, en revanche, les formes sel d'addition d'acide sont converties en base libre par un traitement avec une base ; et, le cas échéant, la préparation de formes isomères au plan stoechiométrique de ceux-ci.

13. Utilisation selon la revendication 10, dans laquelle le trouble est choisi parmi la déprime, un trouble lié à l'anxiété, un trouble de l'alimentation, une suppression immunitaire induite par le stress, une attaque, la maladie de Cushing, les spasmes infantiles, l'épilepsie, une crise et un état inflammatoire.

14. Utilisation selon la revendication 13, dans laquelle le trouble de l'alimentation est l'anorexie mentale, la boulimie ou le syndrome de l'intestin irritable.